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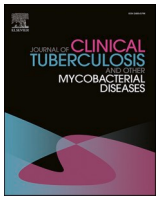

Malnutrition and unsuccessful tuberculosis treatment among people with multi-drug resistant tuberculosis in Uganda: A retrospective analysis

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ABSTRACT

Rationale: Multi-drug-resistant tuberculosis (MDR-TB) poses a significant public health challenge to the control and successful eradication of TB globally. Suboptimal treatment outcomes are common among persons with MDR-TB necessitating a need to understand the contextual factors.
Objective: We determined the factors associated with unsuccessful TB treatment among persons with MDR-TB at a large TB Unit in Central Uganda.
Methods: We retrospectively reviewed medical records for all persons with MDR-TB at Mubende Regional Referral Hospital MDR-TB Clinic in Central Uganda. The patients were treated with either second-line, modified second-line, or individualized anti-TB regimens and completed treatment between January 2012 and October 2023. The primary outcome was unsuccessful TB treatment defined as death, treatment failure, or loss to follow-up and measured as a binary outcome. We used a multivariable binary logistic regression analysis to determine the factors independently associated with unsuccessful TB treatment at a 5 % statistical significance level. We reported the adjusted odds ratio (aOR) and the 95 % confidence interval (CI).
Measurements and results: We analyzed data from 98 persons with MDR-TB who were aged 15–78 years (mean 36.4 ± 15.4 years). Of these, 40 (40.8 %) were cured, 25 (25.5 %) completed TB treatment, 1 (1.0 %) had treatment failure, 13 (13.3 %) died, and 19 (19.4 %) were lost to follow-up. Overall, 33 (33.7 %) participants had unsuccessful TB treatment which was associated with older age for a 1-year increase in age (aOR 1.05, 95 % CI 1.01–1.09), malnutrition—mid-upper arm circumference of <12.5 cm (aOR 2.99, 95 % CI 1.16–7.98), and previous TB treatment (aOR 0.28, 95 % CI 0.10–0.77).
Conclusion: Unsuccessful TB treatment is high among persons with MDR-TB at this TB Unit. It is more likely as age advances and when persons with MDR-TB have malnutrition, but less likely when they have been previously treated for TB. Therefore, interventions to improve treatment outcomes may be beneficial for persons with MDR-TB who are older, malnourished, and those newly diagnosed with the disease. For example, routine nutritional assessment and counseling, including nutritional support for malnourished persons with MDR-TB may be needed to optimize their TB treatment success.

1. Introduction

Tuberculosis (TB) causes an estimated 1.3 million deaths every year [1]. Globally, in 2022, an estimated 410,000 people fell ill with multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB), mostly from sub-Saharan Africa [2]. MDR/RR-TB was estimated to be 3.3 % among the new cases and 17 % among those previously treated for TB [2]. MDR-TB in particular has a devastating effect on individuals and their families, with 50 % of people with TB and their families facing catastrophic costs (more than 20 % of annual household income spent on TB) [2], far off the World Health Organization (WHO) WHO End TB Strategy target of zero catastrophic costs faced by families affected by TB [3].

According to the 2023 Global TB Report, the global treatment success rate among persons with MDR/RR-TB is at 63 % despite the advances in diagnostics and treatments [2]. In Uganda, the treatment success rate for persons with drug-resistant TB was 64 % in 2019/2020, slightly lower than the 66 % observed in the preceding year and nearly 30 % lower than the desired treatment success rate target of 90 % or more in 2024/2025 [4]. The suboptimal TB treatment success rate

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which exemplifies significant gaps in the MDR-TB Control Program across several countries, including Uganda should be a concern as it complicates progress towards ending the global TB epidemic by 2035. Some studies conducted in Uganda have reported previous exposure to second-line anti-TB drugs and severe anemia as factors associated with suboptimal treatment outcomes among persons with MDR-TB [5,6]. In other countries, studies show that infection with human immunodeficiency virus (HIV) [7], the mode of anti-TB treatment delivery [8], being male, aged ≥60 years, and having comorbidities [9] are some of the factors associated with unsuccessful TB treatment among persons with MDR-TB.

Mubende Regional Referral Hospital is one of the MDR-TB Treatment Units in Uganda. The treatment success rate among persons with MDR-TB at the MDR-TB clinic based on program data remains uncertain but could be influenced by various factors that are yet to be established. An in-depth analysis of the individual-level MDR-TB program data provides useful insights into patient-level factors that might explain unsuccessful TB treatment among persons with MDR-TB. Therefore, we described the TB treatment outcomes and analyzed the factors associated with unsuccessful MDR-TB treatment at the Mubende Regional Referral Hospital MDR-TB Clinic in Central Uganda. The information from this study has the potential to inform the strategies to optimize the MDR-TB treatment success rate at the MDR-TB clinic and other similar resource-limited settings elsewhere.

2. Methods

2.1. Study design, setting, and population

We conducted a retrospective review of medical records for persons with MDR-TB at the Mubende Regional Referral Hospital MDR-TB Clinic in Central Uganda. We retrospectively abstracted data for all persons with MDR-TB who had completed treatment between January 2012 and October 2023 from the Health Management Information System (HMIS) TB 016 drug-resistant TB register, a government-managed health information system. The data were abstracted by the HMIS focal person. We considered all persons with MDR-TB within the review period provided TB treatment had been completed. Persons with MDR-TB with unknown treatment outcomes, especially those transferred to other health facilities and those without a record of treatment outcome in the TB register were excluded.

We abstracted data on socio-demographic factors such as age in years that we later categorized as 15–34, 35–44, and 45–78 years, sex as male or female, and residence measured as urban or rural. The data on clinical factors included the past TB treatment history, and nutritional status measured using the mid-upper arm circumference (MUAC) as red (<11.5 cm), yellow (11.5–12.49 cm), and green (12.5–26.5 cm) to signify severe, moderate, and no malnutrition. We combined the categories of individuals with moderate or severe malnutrition to form the category of malnourished persons with MDR-TB, and we compared them with well-nourished persons with MDR-TB. MUAC measurements were used because in routine TB care, the measurements are commonly done by health workers given that it is cheaper and simpler to perform when compared with measuring the body mass index or BMI [10]. Furthermore, the use of MUAC measurement is justified by several studies that show MUAC and BMI measurements are similar [10–13], and MUAC measurements have been extensively used to study malnutrition in people with TB in several settings [14–16] including in Uganda [17,18].

The other clinical factors included the GeneXpert test results, TB treatment model (health facility versus community-based directly observed therapy short course), treatment supporter availability (yes or no), the type of treatment supporter (health worker, community volunteer, and family member), HIV serostatus (positive or negative), and the category of anti-TB regimens measured as second-line TB treatment regimen, modified second-line TB treatment regimen, and individualized TB treatment regimen.

2.2. Variables and measurements

The primary outcome was unsuccessful TB treatment defined as death, treatment failure, or loss to follow-up, expressed as a binary outcome. Independent variables included age categories in years, sex, residence, nutritional status (well-nourished vs. malnourished), category of persons with MDR-TB, treatment supporter availability, and HIV serostatus.

3. Statistical methods

3.1. Sample size estimation and power analysis

We used all the available data so sample size calculation was not applicable. We hypothesize that malnutrition is associated with unsuccessful TB treatment among persons with MDR-TB. Therefore, we performed a power analysis based on the *a priori* hypothesis to determine whether the study had adequate statistical power to demonstrate an association between malnutrition and unsuccessful TB treatment in the population at a 5 % statistical significance level.

3.2. Data analysis

We summarised numerical data as mean and standard deviation when normally distributed or median and interquartile range when skewed. We summarised categorical data as frequencies and percentages. In the bivariate analysis, we cross-tabulated categorical data with the outcome variable and tested differences in the outcome variable using the Chi-square test for larger cell counts (≥5) or the Fisher exact test when the cell count was smaller (<5). We used the student's *t*-test to assess mean differences in numerical data between the study outcomes when the data were normally distributed else the Wilcoxon rank-sum test was used. Variables with $p < 0.25$ in the bivariate analysis were considered statistically significant for multivariable analysis. The factors associated with the outcome variable were modeled in a multivariable binary logistic regression analysis, adjusted for both clinically relevant factors and factors with $p < 0.25$ at the bivariate analysis. We reported the unadjusted and adjusted odds ratio (OR) and 95 % confidence interval (CI). The final multivariable model was parsimonious—it had the lowest Akaike Information Criteria.

3.3. Human subjects

Ethical approval for this study was obtained from Clarke International University Research Ethics Committee (CIU-REC) in Kampala, Uganda (reference number CLARKE-2023-870).

4. Results

4.1. Study profile

We retrieved records for 111 persons with MDR-TB who had initiated and completed their TB treatment between January 2012 and October 2023. Of the retrieved records, 13 were excluded for reasons: 7 participants were returned on first-line treatment and 6 participants had no documented TB treatment outcome (Fig. 1). Overall, the data analyzed were for 98 persons with MDR-TB.

4.2. General characteristics of the participants

Of the 98 participants, 46 (46.9 %) were aged 15–19 years, 75 (76.5 %) were male, 78 (79.6 %) were rural residents, 97 (99.0 %) had pulmonary TB, 57 (58.3 %) were newly diagnosed with MDR-TB, and 61 (62.2 %) were well-nourished as shown in Table 1. On average, participants with unsuccessful TB treatment were significantly older compared to those successfully treated for TB: 33.5 (13.8) vs. 42.1

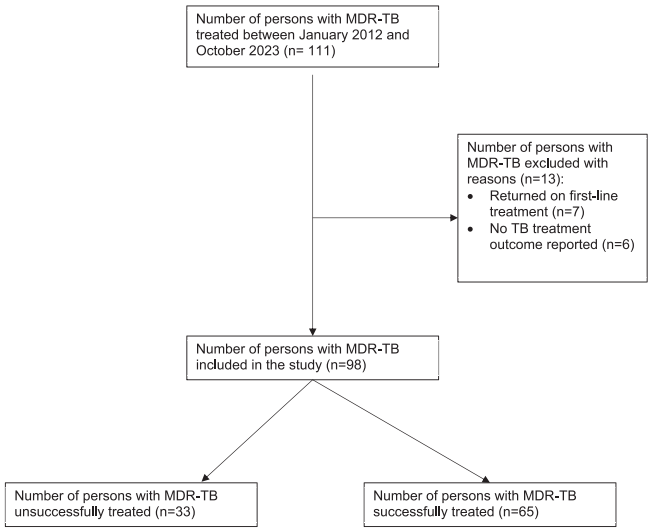

Fig. 1. Shows the study profile for persons with MDR-TB at Mubende Regional Referral Hospital MDR-TB Clinic between January 2012 and October 2023.

(16.9), p = 0.008. Only nutritional status (p = 0.004) showed a statistically significant difference in unsuccessful TB treatment. Supplementary Table 1 shows the drug-susceptibility testing (DST) findings.

4.3. Description of TB treatment outcomes

Of the 98 participants, 40 (40.8 %) were cured, 25 (25.5 %) completed TB treatment, 1 (1.0 %) had treatment failure, 13 (13.3 %) died, and 19 (19.4 %) were lost to follow-up. Overall, 33 (33.7 %) participants had unsuccessful TB treatment.

4.4. Factors associated with unsuccessful TB treatment at the unadjusted and adjusted analyses

In the unadjusted analysis (Table 2), unsuccessful TB treatment was more likely among malnourished persons with MDR-TB compared to well-malnourished persons with MDR-TB (OR 3.54, 95 % CI 1.49–8.70), every 1-year increase in age (OR 1.04, 95 % CI 1.01–1.07), and previous TB treatment (OR 0.39, 95 % CI 0.15–0.93). Variables such as sex, residence, treatment supporter availability, and HIV showed no association with unsuccessful TB treatment. In the multivariable analysis, we found that unsuccessful TB treatment was more likely among malnourished persons with MDR-TB compared to well-nourished persons with MDR-TB (aOR 3.45, 95 % CI 1.35–9.21), increasing age (aOR 1.05, 95 % CI 1.01–1.09), and previous TB treatment (aOR 0.28, 95 % CI 0.10–0.77). The remaining variables were not associated with unsuccessful TB treatment.

4.5. Sensitivity power analysis

In sensitivity power analysis based on effect size from the outcome, our study showed a 23 % (14/61) unsuccessful TB treatment among well-nourished persons with MDR-TB compared to a 51.5 % (19/37) unsuccessful TB treatment among those who were malnourished. Therefore, at a 5 % statistical significance level, our study showed a 76 % statistical power to detect a statistically significant association between malnutrition and unsuccessful TB treatment in the population.

5. Discussion

We investigated the magnitude of unsuccessful TB treatment among persons with MDR-TB at a large referral hospital in Central Uganda. We found that 34 % of them had an unsuccessful TB treatment outcome.

Table 1
General characteristics of the participants stratified by unsuccessful TB treatment.

Variable	Level	Overall (n = 98)	Unsuccessful TB treatment		P-value
			No (n = 65)	Yes (n = 33)	
Age group (years)	15–34	46 (46.9)	30 (46.2)	16 (48.5)	0.172
	35–44	25 (25.5)	20 (30.8)	5 (15.2)	
	45–78	27 (27.6)	15 (23.1)	12 (36.4)	
	mean (SD)	36.4 (15.4)	33.5 (13.8)	42.1 (16.9)	0.008
Sex	Male	75 (76.5)	52 (80.0)	23 (69.7)	0.376
	Female	23 (23.5)	13 (20.0)	10 (30.3)	
Residence	Rural	78 (79.6)	50 (76.9)	28 (84.8)	0.513
	Urban	20 (20.4)	15 (23.1)	5 (15.2)	
Category of TB disease	Pulmonary TB	97 (99.0)	64 (98.5)	33 (100.0)	1.000
	Extrapulmonary TB	1 (1.0)	1 (1.5)	0 (0.0)	
Category of persons with MDR-TB	New	57 (58.2)	33 (50.8)	24 (72.7)	0.062
	Previously treated with first/second-line drugs	41 (41.8)	32 (49.2)	9 (27.3)	
Risk categories	TB contact	19 (19.4)	8 (12.3)	11 (33.3)	0.085
	Fisher folks	1 (1.0)	1 (1.5)	0 (0.0)	
	Diabetic patient	2 (2.0)	1 (1.5)	1 (3.0)	
	Miner	6 (6.1)	5 (7.7)	1 (3.0)	
	Tobacco user	3 (3.1)	2 (3.1)	1 (3.0)	
	HIV infected	9 (9.2)	9 (13.8)	0 (0.0)	
	Others (++)	58 (59.2)	39 (60.0)	19 (57.6)	
GeneXpert results	MTB detected (rifampicin resistance indeterminate)	2 (2.0)	1 (1.5)	1 (3.0)	0.135
	MTB detected (rifampicin resistance detected)	89 (90.8)	57 (87.7)	32 (97.0)	
	MTB trace detected (rifampicin resistance indeterminate)	7 (7.1)	7 (10.8)	0 (0.0)	
Malnourished	No	61 (62.2)	47 (72.3)	14 (42.4)	0.004
	Yes	37 (37.8)	18 (27.7)	19 (57.6)	
Type of DOTS	Facility DOTS	96 (98.0)	64 (98.5)	32 (97.0)	1.000
	Community DOTS	2 (2.0)	1 (1.5)	1 (3.0)	
Category of anti-TB regimens	Second-line treatment regimen	42 (42.9)	28 (43.1)	14 (42.4)	0.493
	Modified second-line treatment regimen	43 (43.9)	28 (43.1)	15 (45.5)	
	Individualized treatment regimen	12 (12.2)	9 (13.8)	3 (9.1)	
	Not reported	1 (1.0)	0 (0.0)	1 (3.0)	
Type of treatment supporter	Health workers	8 (8.2)	6 (9.2)	2 (6.1)	0.842
	Community Volunteer	1 (1.0)	1 (1.5)	0 (0.0)	
	Family member	26 (26.5)	17 (26.2)	9 (27.3)	
	Not reported	63 (64.3)	41 (63.1)	22 (66.7)	
Treatment supporter availability	No	63 (64.3)	41 (63.1)	22 (66.7)	0.899

(*continued on next page*)

Table 1 (*continued*)

Variable	Level	Overall (n = 98)	Unsuccessful TB treatment		P-value
			No (n = 65)	Yes (n = 33)	
	Yes	35 (35.7)	24 (36.9)	11 (33.3)	
HIV status	Negative	62 (63.3)	42 (64.6)	20 (60.6)	0.867
	Positive	36 (36.7)	23 (35.4)	13 (39.4)	

Note: DOTS: Directly Observed Therapy Short Course; SD: Standard deviation; ++: denotes that the participant does not fall in any of the following risk categories: health worker, mentally ill, TB contact, prisoner, refugee, uniformed personnel, fisher folks, diabetic patient, miner, tobacco user, and HIV infected; MTB: *Mycobacterium Tuberculosis.*

Table 2
Factors associated with unsuccessful TB treatment at the unadjusted and adjusted analyses.

Variables	Level	Univariable analysis OR (95 % CI)	Multivariable analysis aOR (95 % CI)
Age group (years)	One-year increase	1.04* (1.01–1.07)	1.05* (1.01–1.09)
Sex	Male	1	
	Female	1.74 (0.66–4.54)	
Malnourished	No	1	1
	Yes	3.54** (1.49–8.70)	2.99* (1.16–7.98)
Residence	Rural	1	
	Urban	0.60 (0.18–1.72)	
Category of persons with MDR-TBTreatment supporter availability	New	1	1
	Previously treated with first/ or second-line drugs	0.39* (0.15–0.93)	0.28* (0.10–0.77)
	No	1	1
	Yes	0.85 (0.35–2.04)	0.92 (0.33–2.54)
HIV serostatus	Negative	1	1
	Positive	1.19 (0.49–2.81)	1.36 (0.51–3.67)

Note: Statistical significance codes at a 5 % level: *p < 0.05; **p < 0.01; OR: Crude odds ratio; aOR: Adjusted odds ratio.

Unsuccessful TB treatment is more likely as age advances and among those with malnutrition, but less likely in persons who have previously been treated for TB. Globally, the magnitude of unsuccessful TB treatment for persons with MDR-TB is 37 % based on the 2023 Global TB Report [2]. Previous studies conducted in Uganda also show almost similar results: a 28.2 % unsuccessful TB treatment in a retrospective review of data from 1,122 persons with MDR-TB across 16 sites between 2014 and 2018 [5] and a 28.6 % unsuccessful TB treatment outcome in a retrospective review of data from 276 persons with MDR-TB across 16 health facilities [6]. For persons with MDR-TB, the World Health Organization recommends a treatment success of ≥75 % [19]. The 34 % unsuccessful TB treatment outcome observed in this study may be considered as being high when compared with the WHO's desired target of 25 % or less.

The unsuccessful treatment outcome in this study mainly resulted from death (13.3 %) and loss to follow-up (19.4 %) compared to treatment failure (1.0 %). This is consistent with previous studies conducted in Ethiopia, with one study showing that loss to follow-up was 13.8 %, mortality at 9.2 %, and treatment failure at 3.1 % as distribution of unsuccessful treatment outcome among 51 persons with MDR-TB [19]. Another study among 89 unsuccessfully treated persons with MDR-TB showed this was mostly due to death (9.3 %) and lost to follow-up (6.9 %) and not treatment failure (3.1 %) [20]. Similarly, high proportions of death and loss to follow-up compared to treatment failure have been reported in studies conducted in Pakistan [9] and China [21], which are countries highly burdened by TB.

Within our context, there is therefore a need to identify the risk factors for mortality and loss to follow-up among persons with MDR-TB in future operational research in order to inform the design of relevant measures for improving the TB treatment success rate. Overall, the present finding indicates a sub-optimal performance of the TB Control Program, which should be a concern as unfavorable treatment outcome is associated with increased TB transmission at the household and community levels, including exacerbating the risk for TB complications and mortality at the individual level.

The association between malnutrition and unsuccessful TB treatment among persons with MDR-TB in Uganda has been understudied. Our finding that unsuccessful TB treatment is more likely among malnourished persons with MDR-TB compared to well-nourished persons with TB is fairly novel considering limited studies have been conducted on this topic in Uganda. In the past, only two studies showed that moderate and severe anemia (a form of micronutrient deficiency) is associated with lower TB treatment success rate among persons with MDR-TB [5,6]. More recently, among retreatment persons with drug-susceptible TB, malnutrition as measured by the mid-upper arm circumference (MUAC) at baseline has been shown to reduce treatment success and sputum smear conversion [17]. Consistent with our findings, one systematic review and *meta*-analysis conducted in Ethiopia showed that undernutrition is associated with a longer time to culture conversion and a higher likelihood of mortality as well as unsuccessful TB treatment among persons with MDR-TB [22]. Additionally, an individual patient data *meta*-analysis showed that being underweight as measured by BMI compared to having normal weight is associated with a higher likelihood of unsuccessful TB treatment, including mortality and treatment failure among persons with rifampicin-resistant TB [23].

Our finding is biologically plausible because malnutrition slows immune recovery, decreases drug absorption, and increases the likelihood of drug toxicities hence hindering the effectiveness of anti-TB treatment regimens and potentially leading to unfavorable TB treatment outcomes. The finding underscores the need to tackle malnutrition among persons with MDR-TB, including routine nutritional assessment, counseling, and support. Whereas nutritional supplementation could improve weight gain during TB treatment and accelerate sputum smear conversion and subsequently treatment success, such interventions are lacking across most TB Control Programs. However, nutritional support is crucial for better TB treatment outcomes, requiring no further emphasis.

For every one-year increase in age, unsuccessful TB treatment is 5 % more likely to occur. This finding is consistent with several studies that show unsuccessful TB treatment is likely as age increases. One study conducted at Mbarara Regional Referral Hospital [24] and another in Pakistan [9] both showed that persons with MDR-TB over 60 years old are more likely to experience unsuccessful treatment. Another retrospective cohort study conducted in Ethiopia also showed that persons with MDR-TB aged over 44 years are more likely to experience unsuccessful TB treatment [20]. This finding could be attributed to lower immunity resulting from aging, making individuals more vulnerable to infectious diseases and comorbidities such as malignant conditions, malnutrition, and other age-related health conditions including slowing recovery from TB disease. These factors favor unsuccessful TB treatment outcomes and its complications [25]. Therefore, older persons with MDR-TB may benefit from close monitoring of their health condition, including factors contributing to unsuccessful treatment, such as non-adherence to anti-TB treatment.

We found previous TB treatment is associated with a lower likelihood of unsuccessful TB treatment among persons with MDR-TB contrary to findings in a past study. Previous TB treatment results from factors such as incomplete or inadequate treatment and poor treatment adherence

[26]. Individuals with a previous history of TB treatment might have a better understanding of TB treatment requirements and can address barriers to non-adherence thus reducing the likelihood of unsuccessful TB treatment compared to those newly diagnosed with MDR-TB.

6. Study strengths and limitations

Our study has some strengths and limitations. We employed a rigorous analytic approach to ensure credible findings as the regression model was *a priori* specified. Our study had a 76 % statistical power, which is adequate to detect an association between malnutrition and unsuccessful TB treatment in the population. The study limitations include a small sample size even after retrieving all available data. However, compared to most single-site studies focused on persons with MDR-TB in sub-Saharan Africa, our sample size is large. As secondary data were analyzed, the possibility of recording and transcription errors cannot be ignored. Also, there are several unmeasured confounders such as the baseline weight, socioeconomic status like alcohol consumption, and several clinical factors like culture conversion and hemoglobin, including several other unknown confounders.

For example, we did not analyze data on adherence to anti-TB treatment and adverse effects. Moreover, both non-adherence to anti-TB treatment [27] and adverse effects [28] are prevalent among persons with MDR-TB and have been shown in previous studies as being associated with unsuccessful TB treatment. Additionally, MUAC was measured as a categorical variable rather than as a continuous variable and this potentially leads to loss of information and statistical efficiency. These limitations should be considered in the interpretations of the findings.

7. Conclusions and recommendations

We found that a higher proportion of persons with MDR-TB have unsuccessful TB treatment. Unsuccessful TB treatment is more likely as age advances and among those with malnutrition, but less likely in persons previously treated for TB. Interventions to improve treatment outcomes may be beneficial for persons with MDR-TB who are older, malnourished, and newly diagnosed with the disease. For example, routine nutritional assessment and counseling, including nutritional support for malnourished persons with MDR-TB may be needed to optimize the TB treatment success.

CRediT authorship contribution statement

Samuel Engoru: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Francis Bajunirwe:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Jonathan Izudi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2024.100477.

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